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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/511,719	KIM ET AL.	
	Examiner	Art Unit	
	Christine Foster	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17-32* is/are pending in the application.

4a) Of the above claim(s) *24 and 32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-23 and 25-31* is/are rejected.

7)☒ Claim(s) *17-21,23,25-29 and 32* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 10/18/04
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, claims 17-25 in the reply filed on 8/11/06 is acknowledged. The elections of the species of **diabetic renal disease** as the disease to be diagnosed, **SEQ ID NO:3** as the recombinant protein of βig-h3, **antibody** as the ligand, and of **ELISA** as the type of assay method are further acknowledged.

2. The traversal is on the ground(s) that Applicant disagrees with the Examiner's characterization of the special technical feature linking Groups I and II (Applicant's response, p. 3). Specifically, Applicant argues that use of βig-h3 or βig-h3 fas-1 domains, their fragments or derivatives to diagnose specific diseases as recited in claim 17 represents a single general inventive concept linking Groups I and II. Applicant's arguments are persuasive, and the requirement for restriction between Groups I and II is hereby withdrawn.

However, regarding the **election of species** requirements, Applicant argues that a search of all species would not be unduly burdensome and points to MPEP 808.01 (Applicant's response, p. 4-5). This is not found persuasive because Applicant is referring to the requirement to demonstrate search burden that pertains to applications filed under 35 U.S.C. 111(a) (see MPEP 801). There is no corresponding requirement to demonstrate search burden in applications filed under 35 U.S.C. 371.

The requirement is still deemed proper and is therefore made FINAL. Lack of unity will be reassessed at each stage of prosecution hereafter.

3. Applicant's response did not include an identification of claims reading on the elected species. However, the Examiner has determined that claims 24 and 32 do not read on the elected

species of **SEQ ID NO:3**. Accordingly, claims 24 and 32 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions/species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 8/11/06.

4. Claims 17-32 are pending in the application, with claims 24 and 32 currently withdrawn.

Specification

5. The specification is objected to for the following reasons:

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1 .821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1 .821 through 1 .825 for the reason(s) set forth below.

It appears that while Applicant has successfully submitted sequences in a computer readable form, the specification is not compliant with sequence rules. **For example, page 7, line 1 of the instant specification refers to amino acid sequences that are not accompanied by SEQ ID numbers.**

Applicant is required to review the instant application for compliance with the requirements of applications which contain sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821-1.825.

If the noted sequence(s) is in the sequence listing filed, Applicants must amend the specification to identify the sequence appropriately by SEQ ID NO. If the noted sequence(s) is not in the sequence listing as filed, Applicants must provide (1) a substitute copy of the sequence

listing in both computer readable form (CRF) and paper copy, (2) an amendment directing its entry into the specification, (3) a statement that the content of the paper and CRF copies are the same and, where applicable, include no new matter as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d), and (4) any amendment to the specification to identify the sequences appropriately by SEQ ID NO.

Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g).

Applicant's time to comply with the sequence rules is set forth on the attached Office Action Summary (Form PTOL-326). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a). In no case may an applicant extend the period for reply beyond the SIX MONTH statutory period. Direct the reply to the undersigned.

6. The use of trademarks (TRITON, TWEEN) has been noted in this application (see at p. 30, 32, 34). They should be capitalized wherever they appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Objections

7. Claims 17-21, 23, 25-29, and 32 are objected to because of the following informalities:

8. Claim 17 recites the abbreviation "βig-h3". It is suggested that in the first instance of an abbreviation in the claims that the abbreviation be accompanied by the full term. Similarly:

Claim 20 recites the abbreviations "ELISA" and "RIA".

Claim 21 recites the abbreviation "OD".

Claims 17, 23, and 31 recite the abbreviation "fas-l".

9. Claim 17 is objected to because it refers to "the above step 1" and "the above step 2", yet the steps of the method have been designated as a, b, c rather than numerically.

10. Similarly, claim 19 is objected to because it refers to "step 3)", which is not clear since there is no step so designated in claim 17.

11. Similarly, claim 21 refers to "the above step 1", "step 1", "step 2", and "the above step 3". In addition, the reference to "**the above step**..." is confusing since the steps apparently referred to appear in claim 17; since there are a number of intervening claims it is suggested that if this terminology be employed that the claims clearly state which *claim*, as well as which step, is being referred to.

12. In claims 18, 20, 27, and 32 it is suggested that the standard Markush language "selected from **the** group consisting of" be employed.

13. Claim 19 is objected to because it refers to "the specific binding reaction", yet claim 17 refers only to a "binding reaction" and not to a "specific binding reaction".

14. Claim 21 appears to require the article "a" before the word "matrix" in step (a). The claim also appears to require an article such as "a" or "the" before the word "antibody" in step (b).

15. Claim 25 is objected to because it recites that the sample can be "any body fluid including urine, blood, or synovial fluid", which is ambiguous since it implies that the sample merely **includes** one of these fluids, while the specification indicates that the sample should **be** one of these fluids.

16. Claim 26 is object to for grammatical reasons in that it recites a "kit for the renal diseases...". It is suggested that the claim recite a kit for the "*diagnosis* of renal diseases...".

17. Claims 26-28 are objected to because claim 26 refers to "ligands" in the plural while claims 27-28 refer to "the ligand" in the singular.

18. Claim 26 is objected to because as a result of the wording describing the components of the kit. It would seem that the claim is drawn to two components, (1) "βig-h3 protein or recombinant proteins of fas-l domain in the βig-h3 protein or fragments or derivatives thereof" and (2) ligands of (1). However, because of the way that the claim is worded it may present for confusion.

19. Claim 27 is objected to because the wording is confusing and may imply that the Markush group members are (1) "antibody specifically binding to βig-h3 protein" (2) fas-l domain of βig-h3, etc. while it would seem that the claim intends to recite that the ligand is an antibody capable of binding to βig-h3, fas-l domain of βig-h3, etc.

20. Claim 28 appears to require the article "an" before the word "antibody".

21. Claim 29 is objected to because the term "coloring substrate" appears to be the result of a translation error of "colorimetric substrate". Applicant may also wish to correct this term in the specification; the examiner would note that this would constitute correction of an obvious error and would not be considered new matter.

Claim Rejections - 35 USC § 112

22. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

23. Claims 1-23 and 25-31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Written Description

24. Claim 17 recites "recombinant proteins of βig-h3 or βig-h3 fas-l domains, **their fragments or derivatives,** as standard proteins" (emphasis added). The claim also recites "specific ligands against the above proteins, **their fragments or derivatives**". Claim 26 similarly recites "βig-h3 protein or recombinant proteins of fas-l domain in the βig-h3 protein **or fragments or derivatives thereof**" as well as "their ligands".

The specification does not provide a written description to support evidence of possession of the genus of **fragments or derivatives** of βig-h3 proteins or of the genus of **ligands** thereof.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed. The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the application. These include "level of skill

and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention." MPEP 2163.

Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co. The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, or chemical name', of the claimed subject matter sufficient to distinguish it from other materials." Id. at 1567, 43 USPQ2d at 1405. The court also stated that:

> a generic statement such as "vertebrate insulin CDNA" or "mammalian insulin CDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. at 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAS might be described. "A description of a genus of cDNAS may be achieved by means of a recitation of a representative number of cDNAS, defined by nucleotide sequence, falling within the scope of the

genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem. Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that "the written description requirement can be met by show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics; i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." Id. at 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

Although the inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here. A disclosure that does not adequately describe a product itself logically cannot adequately describe a method of using that product.

The instant specification may provide an adequate written description of the genus of **fragments or derivatives** of βig-h3 or βig-h3 fas-1 domains, per Lilly by structurally describing representative fragments/derivatives or by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus." Alternatively, per Enzo, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics

when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

However, the instant specification does not describe the genus of βig-h3 or βig-h3 fas-l domains, their fragments or derivatives in a manner that satisfies either the Lilly or Enzo standards. Although the specification discloses human βig-h3 (SEQ ID NO:3), it does not disclose what portions of this protein are responsible for binding to specific ligands (e.g. antibodies), and therefore does not disclose what sequences, modifications or fragments of SEQ ID NO:3 would retain immunological reactivity with the antibodies. Since the specification fails to adequately describe the genus of **fragments or derivatives of βig-h3 or βig-h3 fas-l domains**, it also fails to adequately describe the method in **fragments or derivatives** of these proteins are used as standards.

25. In addition, claims 18 and 27 recite that the specific ligands of βig-h3 or βig-h3 fas-l domains may be antibodies, **RNA, DNA, lipids, proteins, organic compounds, and inorganic compounds** (emphasis added). The specification describes production of antibodies against □ig-h3 using art-recognized techniques (Example 1). However, the specification does not describe production of ligands against βig-h3 that are **RNA, DNA, lipids, proteins, organic compounds, or inorganic compounds**. The specification fails to disclose any partial structure, relevant identifying characteristics, or method of making specific ligands that are RNA, DNA, lipids, proteins (other than antibodies), organic compounds, or inorganic compounds. Further, the specification fails to disclose any correlation between structure of the recited ligands and function (ability to bind βig-h3). Accordingly, in the absence of sufficient recitation of

distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus of non-antibody ligands.

Enablement

26. Claims 17-23 and 25-31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The nature of the invention relates to the observation that the protein βig-h3 is differentially expressed in certain disease states, including hepatocirrhosis, microalbuminuria, and rheumatoid arthritis.

The claims are drawn to methods and kits for diagnosing all renal diseases, all hepatic diseases, all cardiovascular diseases, as well as rheumatoid arthritis based on measurement of βig-h3 in all types of samples.

With respect to diagnosis of "renal diseases", the specification teaches measurement of βig-h3 levels in subjects with type II diabetes (Example 4). Applicant's report that βig-h3 in urine was increased these subjects as compared to normal subjects (Table 1). The specification further teaches that in diabetic subjects with the renal diseases microalbuminuria, overt proteinuria, or chronic renal failure that βig-h3 levels were increased over diabetic subjects without renal failure (Table 1). However, this is not a teaching that is commensurate in scope with the breadth of the claims, since the finding of increased βig-h3 in the urine of type II diabetic subjects does not predictably enable one skilled in the art to carry out diagnosis of all

renal diseases. Attached is the table of contents for the book "Atlas of Diseases of the Kidney" (R.W. Schrier, Ed., 1999 by Current Medicine, Inc., downloaded from www.kidneyatlas.org), which teaches that diseases of the kidney include not only "diabetic kidney disease" as taught in the specification but also nephrotoxic acute renal failure, glomerulonephritis, vasculitis, tubulointerstitial disease, and others. The specification provides no direction or guidance with respect to diagnosis of these various renal diseases, which differ with respect to etiology, symptoms, pathogenesis and course of disease.

Similarly, the claims encompass diagnosis of all "hepatic diseases", yet the specification teachings relate only to hepatocirrhosis (Example 5), which is not a teaching that would predictably enable the diagnosis of Alagille syndrome, biliary atresia, autoimmune hepatitis, and the various other disease of the liver that are claimed (see Columbia University Department of Medicine, list of "Diseases of the Liver", downloaded from www.cumc.columbia.edu/dept/medicine/divisions/gi/disliv.html on 10/14/2006).

Further, in light of the broad scope of diseases currently claimed, the specification fails to enable one skilled in the art to diagnose any one of these diseases since the specification fails to provide direction or guidance with respect to differential diagnosis. In other words, if hundreds of different diseases can be diagnosed based on βig-h3 levels, how would one skilled in the art know which of these diagnoses to confer on a subject that had altered βig-h3 levels? Would high or low βig-h3 levels be indicative of disease, and of which disease? The specification simply fails to provide sufficient direction or guidance commensurate with the scope of the claims.

The examiner further notes that claims are broad not only with respect to the large number of diseases to be diagnosed, but also with respect to the type of body sample in which

βig-h3 is to be measured. As noted above with respect to renal disease, the specification teaches in Example 4 that βig-h3 levels in urine were increased in some type II diabetes subjects that also had renal disease. However, such a teaching fails to enable one skilled in the art to carry out diagnosis of renal disease based on βig-h3 levels in all types of body samples. LaBaer et al. ("So, You Want to Look for Biomarkers (Introduction to the Special Biomarkers Issue)" Journal of Proteome Research 2005, 4, 1053-1059) teaches that relevant biomarkers may be present only at very low concentration in easily accessible fluids such as blood, saliva, or urine, and therefore masked by much more abundant unrelated proteins (p. 1057, right column, the section beginning "Sample Considerations"). Furthermore, the specification fails to teach that βig-h3 levels all body samples types can be used to diagnose all of the claimed diseases. For example, the specification fails to disclose that βig-h3 levels in synovial fluid are altered in diabetic renal disease and can be used for diagnosis as claimed in claim 25. Conversely, if urine βig-h3 levels are indicative of diabetic renal disease, it is unclear how urine βig-h3 levels could also be used to diagnose rheumatoid arthritis.

Furthermore, in light of Applicant's own postfiling work, it is clear that one skilled in the art would not be able to carry out diagnosis of all diseases based on βig-h3 levels in all types of body samples. Ha et al. ("Elevation of urinary βig-h3, transforming growth factor-β-induced protein in patients with type 2 diabetes and nephropathy" *Diabetes Research and Clinical Practice* **65** (2004) 167-173) teach that there is "no significant difference in plasma βig-h3 levels" between normal control, diabetic, and diabetic with renal disease populations (Table 1 and p. 171, left column, the first paragraph). Thus, one skilled in the art would not expect to be able to successfully diagnose diabetic renal disease using plasma samples.

With regard to the elected species of "diabetic renal disease", the examiner would further note that specification fails to provide sufficient direction or guidance because it may be seen in Table 1 that βig-h3 levels were increased even in those diabetic subjects *without* renal disease (Table 1, "Type II DM population"), which appears to represent a false positive finding. The specification notes this finding at p. 38, line 14 to p. 39, line 5, but concludes from this that βig-h3 is an early marker of renal disease since it is detectable in the absence of any clinical symptoms of renal disease. However, one skilled in the art would not accept such a conclusion without question, since when investigating a biomarker for validity in diagnosis of disease, the finding of that biomarker in the absence of disease would normally be considered to be a false positive until this could be ruled out by further experimentation. See LaBaer et al. (discussed above) at Figure 1 in particular. LaBaer et al. further teach that for biomarkers to be used for diagnosis, quantitative values must be established that set the boundary between a positive and negative test (see p. 105, "Disease Diagnosis"). The specification fails to teach such "cutoff" values with respect to diagnosis of diabetic renal disease or any of the other claimed diseases to be diagnosed.

Furthermore, the examiner would also note that while the data in Table 1 show a distinction between βig-h3 levels in normal subjects as compared to type II diabetic subjects (those with and without renal disease), the distinction between βig-h3 levels in diabetic subjects without renal disease (the second table entry) and those with renal disease (the third, fourth and fifth table entries) is less apparent, being within the reported margins of error. In other words, while the data show a clear separation between βig-h3 levels in diabetes vs. normal subjects, it would appear that with respect to the populations of diabetic vs. diabetic with renal disease that

the separation is not statistically significant. For example, compare "Type II DM" (without renal disease) βig-h3 levels of 101.9 with "Type II DM + overt proteinuia" (with renal disease) βig-h3 levels of 105.4. These levels are the same within the margins of error reported. As a result, one skilled in the art would not reasonably expect based on these data to be able to diagnose the diabetic renal disease of overt proteinuria (for example), since there is apparently no statistically significant change in disease vs. control subjects.

Therefore, due to the lack of direction/guidance presented in the specification regarding diagnosis of all of the various claimed diseases based on βig-h3 levels, and especially the lack of guidance with respect to differential diagnosis, the lack of working examples directed to same, and the breadth of the claims, the specification fails to teach the skilled artisan how to make and use the claimed invention without undue experimentation.

27. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

28. Claims 1-23 and 25-31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

29. Claims 17-23 and 25 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: a step in which disease is diagnosed. The method objective as recited in the preamble is a method of diagnosing disease, but the body of the claim fails to set forth any steps that achieve this outcome. Step (c) of claim 17 recites "measuring the

amount of βig-h3 protein of samples" but does not refer to diagnosis. It would seem that the **samples** in which the amount of βig-h3 protein is measured would have to be samples from a patient in which disease is to be diagnosed, but the claim fails to recite any correlation between the sample and diagnosis. Further, the claims fail to recite whether increased or decreased amounts of βig-h3 would be indicative of disease.

30. Claim 17 recites the steps of "**preparing** recombinant proteins" and "**preparing** specific ligands" (steps (a) and (b)). The claim is indefinite because the metes and bounds of "preparing" the reagents are unclear. Specifically, it is not clear whether the reagents are actually being *made*, which would involve steps such as transforming DNA into a heterologous source and expressing and purifying the encoded protein in the case of step (a), and immunizing a mammal with antigen and screening hybridomas in the case of step (b), or alternatively whether these reagents are being *provided* for use in the method. For the purposes of examination the references to "preparing" reagents in steps (a) and (b) was assumed to mean that the reagents are "provided" in these steps.

31. Claims 17 and 26-27 recite the limitations "βig-h3 fas-l domains" or "fas-l domain of βig-h3". The specification does not define "βig-h3 fas-l domains", such that the metes and bounds of the claim are unclear. It is unclear what portion or portions (i.e. what specific sequences) of βig-h3 would be considered to comprise "βig-h3 fas-l domains" since the domain boundaries are not specifically described in the specification.

32. Claim 17 recites "measuring the amount of...protein...with **the method**" in step (c). This recitation of "the method" apparently refers back to the "method" recited in the preamble of the claim ("A method for diagnosing..."). This reference to "the method" in the body of the claim is

improper because it is the body of the claim that is responsible for defining the method; the method cannot be defined by reference to itself since it has not yet been fully set forth in the claim.

33. Claim 17 recites "measuring the amount of βig-h3 protein of samples with the method using binding reaction of ligands...with the recombinant proteins, their fragments or derivatives", which is vague and indefinite because the claim does not set forth **how** the ligands and recombinant proteins are used to carry out the measurement step. How does binding between a standard protein and its specific ligand result in measurement of βig-h3 protein in the sample?

34. Claim 20 recites the method of "rapid assay", which is vague and indefinite. The specification discloses a "rapid assay" along with a non-patent literature citation by Kasahara et al. at p. 18, lines 3-4, but does not specifically define "rapid assay". The metes and bounds of the claim cannot be determined because it is unclear what a "rapid assay" would consist of.

35. Claim 21 recites the limitations "the secondary antibody" and "the reactant". There is insufficient antecedent basis for these limitations in the claims.

36. Claim 22 recites the limitation "**the βig-h3 protein**", which is unclear since claim 17 refers not only to " recombinant βig-h3 proteins" in step (a) but also to measuring "βig-h3 protein" in a sample in part (c). It is unclear which of these (or both) claim 22 is referring to.

37. Claim 23 recites the limitation "**the** recombinant βig-h3 proteins comprising 4^{th} fas-1 domains". There is insufficient antecedent basis for this limitation in the claim.

38. In claims 23 and 31 the recitation of "**4^{th} fas-1 domains**" that are "**repeatedly linked**" is also indefinite because the domain boundaries of fas-1 domains are not specifically described in the specification as discussed above. It is unclear what amino acid sequence is being referred to.

The recitation of "repeatedly linked" domains also renders the claims indefinite in the absence of a specific definition for this term, since the metes and bound of the term are unclear. It is unclear what the domains are linked to and what type of linkage is encompassed. Also, it is unclear how just one domain could be "repeatedly linked".

39. Claim 25 is indefinite because it recites that the sample "**can be**" any body fluid, which is not a positive recitation. It is unclear whether the sample is actually one of the recited body fluids or not.

40. Claim 25 is also indefinite because it recites that "the sample can be **any body fluid including urine, blood, or synovial fluid**". A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 25 recites the broad recitation **any body fluid**, and the claim also recites **urine, blood, and synovial fluid,** which are narrower statements of the range/limitation.

Claim Rejections - 35 USC § 102

41. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

42. Claims 26-27 and 29-31 rejected under 35 U.S.C. 102(a), or, alternatively 102(e) as being anticipated by Kim et al. (WO 01/87327 A1).

The applied reference has a common inventor/assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Kim et al. teach a kit comprising βig-h3 proteins and ligands thereof (the integrin α3β1, contained in HCE cells) (see p. 24-26, Example 1-3).

With respect to claim 29, the kit further comprises a colorimetric hexosaminidase substrate (see also p. 21).

With respect to claims 30-31, the reference teaches wild-type human βig-h3 proteins (p. 19-23, Example 1-1). This reads on claim 30 since the full-length protein would comprise SEQ

ID NO:3; note the open language in the claim ("having"). This reads on claim 31 since the full-length protein would also include the 4th fas-l domain (see also p. 16-17 of the reference), which would be considered to be "repeatedly linked" in the absence of a specific definition for this term (see rejection under 112, 2nd paragraph above) in that the domain includes a polymer of amino acids linked together.

It is noted that the intended diagnostic use of the claimed kit as recited in the preamble has not been construed as a claim limitation. See MPEP 2111.02.

Claim Rejections - 35 USC § 103

43. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

44. Claims 26-31 rejected under 35 U.S.C. 103(a) as being unpatentable Harlow & Lane (Antibodies: A Laboratory Manual (1988) Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, pages 558-559, 570-576, 586-589 and 591-593) in view of Gilbert et al. ("Renal expression of transforming growth factor-β-inducible gene-h3 (βig-h3) in normal and diabetic rats" *Kidney International* **54** (1998), 1052-1062) and Zuk et al. (US 4,208,479).

Harlow & Lane teach various assay formats for detecting and quantitating antigens, including antigen competition assays, which employ a sample of pure or nearly pure antigen as a standard, which is mixed with a test sample containing an unknown amount of the antigen to be detected (see especially p. 559, "Detecting and quantitating Antigens", and p. 570). The standard

antigen and the antigen in the test sample compete for binding to a ligand (antibody) that is specific for the antigen. The reference also teaches that samples containing known amounts of pure antigen can also be used to generate standard curves, which can be used to make assays quantitative (p. 576).

The reference teaches detection of antigens in general using such competitive assay formats, but does not teach detection of βig-h3.

Gilbert et al. teach that the expression of βig-h3 is significantly increased in the kidneys of rats with experimentally-induced diabetes (see the entire document, especially the abstract; the paragraph bridging p. 1052-1053; p. 1056-1057, "Discussion"; and p. 1059-1060. Gilbert et al. teach that βig-h3 levels are correlated with those of TGF-β, which is known to play a pathogenetic role in diabetic kidney disease, and further that βig-h3 may be useful as an index of TGF-β1 bioactivity in the kidney (p. 105).

Zuk et al. teach kits, in which reagents used in performing assays are combined together for convenience and for enhancing accuracy (column 22, lines 20-53).

Therefore, it would have been obvious to one of ordinary skill in the art to employ the competition assay format of Harlow & Lane, which employs a sample of the protein to be detected, in order to detect βig-h3 because Gilbert et al. teach that this protein is an index of TGF-β1 bioactivity in the kidney. It would have been further obvious to package all of the reagents necessary for performing such an assay into a kit as taught by Zuk et al. for convenience.

With respect to claim 29, Harlow & Lane teach the buffer/washing solution PBS (e.g. p. 586), secondary antibody (see p. 574-575), chromogenic substrates (p. 592), and stop solution (H2SO4, p. 593).

With respect to claim 30, it is noted that the claim employs open transitional language in reference to the recited sequences ("having"). As Harlow & Lane teach use of purified antigen to be detected in competition with the same antigen that is detected, and because Gilbert et al. teach the full-length βig-h3 protein (see p. 1056), the purified full-length βig-h3 would comprise the sequences recited as well as the 4th fas-1 domain. As a polymer of amino acids, the protein would be considered to be "repeatedly linked" as in claim 31 in the absence of a specific definition for this term in the specification (see rejection under 112, 2nd paragraph above).

It is noted that the intended use of the kit as recited in the preamble has not been construed as a claim limitation. See MPEP 2111.02.

45. Claims 17-23 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable Harlow & Lane in view of Gilbert et al. and Ratti et al. (US 5,629,167).

Harlow & Lane teach various assay formats for detecting and quantitating antigens, including antigen competition assays, which employ a sample of pure or nearly pure antigen as a standard, which is mixed with a test sample containing an unknown amount of the antigen to be detected (see especially p. 558, p. 559 ("Detecting and quantitating Antigens"), and p. 570-573). The standard antigen and the antigen in the test sample compete for binding to a ligand (antibody) that is specific for the antigen. The standard antigen and the antigen in the test sample

compete for binding to a specific ligand (antibody) that is specific for the antigen. The reference does not teach detection of βig-h3 or of diagnosis of diabetic renal disease.

Gilbert et al. teach that the expression of βig-h3 is significantly increased in the kidneys of rats with experimentally-induced diabetes (see the entire document, especially the abstract; the paragraph bridging p. 1052-1053; p. 1056-1057, "Discussion"; and p. 1059-1060. Gilbert et al. teach that βig-h3 levels are correlated with those of TGF-β, which is known to play a pathogenetic role in diabetic kidney disease, and further that βig-h3 may be useful as an index of TGF-β1 bioactivity in the kidney (p. 105).

Therefore, it would have been obvious to one skilled in the art to employ the method of detecting antigens of Harlow & Lane in order to detect βig-h3 since Gilbert et al. teach that βig-h3 may be used as an index of TGF-β1 bioactivity in the kidney. Furthermore, it is well known in the art that proteins or other markers that are differentially expressed in disease as compared to healthy controls can be measured as biomarkers of that disease for the purpose of diagnosis. As such, although Gilbert et al. are not explicit in teaching that βig-h3 can be used to diagnose diabetic kidney disease, based on the teachings in the reference that βig-h3 levels are increased in diabetes, and further that such levels may reflect TGF-β1 bioactivity, which mediates diabetic kidney disease, it would have been obvious to one skilled in the art to diagnose diabetic kidney disease based on measurements of elevated βig-h3 levels.

Regarding the limitation that the protein of step (a) is "recombinant", while Harlow & Lane do not specifically teach that the antigen is produced by recombinant DNA technology, such technology as well as its advantages were well known in the art. For example, Ratti et al. teach a significant advantage of producing protein by recombinant DNA techniques rather than

by isolating and purifying a protein from natural sources is that equivalent quantities of the protein can be produced by using less starting material than would be required for isolating the protein from a natural source. Therefore, it would have been further obvious to prepare the protein antigen by recombinant techniques to obtain larger quantities of protein.

With respect to claim 21, Harlow & Lane teach a competitive assay format where the purified antigen standard is immobilized to a solid phase, reacted with the test solution and labeled antibody, washed to remove unbound antibody and antigen, and then the assay is quantitated by measuring the "optical density" (absorbance) at 450 nm using a horseradish peroxidase-activated chromogenic substrate (see p. 570-573 and 591-593). The reference teaches that the assay may employ a single labeled antibody or alternatively an unlabeled primary antibody and a labeled secondary antibody (p. 572, step iv.).

With respect to claim 22, it is noted that the claim employs open transitional language in reference to the recited sequences ("having"). As Harlow & Lane teach use of purified antigen to be detected in competition with the same antigen that is detected, and because Gilbert et al. teach the full-length βig-h3 protein (see p. 1056), the purified full-length βig-h3 would comprise the sequences recited as well as the 4th fas-1 domain. As a polymer of amino acids, the protein would be considered to be "repeatedly linked" as in claim 23 in the absence of a specific definition for this term in the specification (see rejection under 112, 2nd paragraph above).

With respect to claim 25, the method of Harlow & Lane, Gilbert, and Ratti et al. reads on the claim since it is unclear whether the sample actually is the recited fluids or not (see rejection under 112, 2nd paragraph above).

Conclusion

46. No claims are allowed.

47. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Iaccheri et al. (US 4842995) and Paulse et al. (US 6675104 B2) are cited for relevance to claim 25 for their teaching that blood and urine are easily collected sample types that are available in a relatively high quantity.

48. Gilbert et al. ("Urinary transforming growth factor-β in patients with diabetic nephropathy: implications for the pathogenesis of tubulointerstitial pathology" *Nephrol Dial Transplant* (2001) 16: 2442-2443) is also cited as relevant to the claimed invention for teaching the role of TGF-β (which induces βig-h3) in diabetic renal disease (diabetic nephropathy), similar to Gilbert et al. '98 discussed above.

49. It is noted that this Office Action contains rejections of the same claims under 35 USC 112, 1st (enablement) and 35 USC 103(a). While these rejections may seem contradictory, they are not, because each is based upon a different legal analysis, i.e., sufficiency of the disclosure of the instant application to support claims under 35 USC, 1st paragraph vs. sufficiency of a prior art disclosure to anticipate or render obvious an embodiment(s) of the claimed invention (See *In re Hafner*, 161 USPQ 783(CCPA 1969)).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Foster whose telephone number is (571) 272-8786. The examiner can normally be reached on M-F 8:30-5. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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